REMARKS

The Claims

Applicants have added new claims 19-24. The new claims are supported throughout the specification. See, for example, line 31 on page 18 to line 3 on page 19, and line 7 on page 19. The claim amendments introduce no new matter. Following entry of the new claims, claims 1-11, 13, 14, and 16-24 will be pending.

The Rejections

Applicants thank the Examiner for withdrawing the rejections under 35 U.S.C. §§ 102(b) and 103(a). Applicants address the Examiner's rejections under 35 U.S.C. § 112 below.

35 U.S.C. § 112, first paragraph, written description

Claims 1-11, 13, 14, 16-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner contends that "the specification does not sufficiently describe the genus of compositions encompassed by the claims such that it would be readily apparent to one of skill in the art which compositions had the desired function (the ability to deliver the nucleic acid molecule into a cell) and which ones couldn't without performing additional experimentation" (Office Action, page 4). Applicants traverse.

The specification may satisfy the written description requirement of a claimed genus by reciting a representative number of species falling within the scope of the genus or by describing structural features common to the genus that constitute a substantial portion of the genus (MPEP 2163). Accordingly, an application does not need to actually exemplify each member of the claimed genus in working examples. Here, the specification satisfies the written description requirement.

First and foremost, the specification and claims recite a specific chemical formula (I) for the copolymer of the claimed complex. Thus, under *Fiers v. Revel*, 25 U.S.P.Q.2d 1601 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), the specification does exactly what is required—the compound, not a method of

isolating it, is specifically described. This formula also satisfies *Vas-Cath v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). Certainly, applicants had possession of the claimed invention. Applicants recited in the specification the chemical formula of the compound to use. For these reasons alone, applicants request that the Examiner reconsider and withdraw the "written description" rejection.

Under his "written description" rejection, the Examiner also contends that the application does not teach which compounds work and which do not. Applicants traverse.

Applicants' specification tells the skilled worker which compounds work—compounds of Formula I. The Examiner has pointed to no compounds encompassed by Formula I that do not work. And, the application provides several actual examples of compounds that fall within Formula I that do work. See, e.g., Examples 9-12. Further, the Patent Laws do not require that *every* embodiment encompassed by the claims be an operative embodiment (see MPEP 2164.08(b)). Thus, on this accord also, applicants request that the Examiner reconsider and withdraw the rejection.

35 U.S.C. § 112, first paragraph, enablement

Claims 1-11, 13, 14, 16-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner contends that the specification, while being enabling for the working embodiments provided in the Examples (e.g., PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid P3INF7 (Example 10), DOTAPcholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12)), does not reasonably provide enablement for the entire scope of the claimed invention.

The Examiner argues that there are a number of obstacles that must be overcome when using polymers for delivering nucleic acid molecules into cells. The Examiner cites Finsinger et al. (Gene Therapy 2000 7: 1183-1192 "Finsinger") and Choi et al. (WO 9929839, "Choi") to argue that the problems associated with methods of introducing nucleic acids into cells include opsonization, interaction with solutes, clearance, low transfection efficiency, and precipitation of the nucleic acids. The Examiner additionally argues that because the art teaches only polymers covalently bound into nucleic acid-containing complexes, additional undue experimentation would be required to overcome the obstacles to

enable nucleic acid delivery using a charged copolymer bound in a complex via ionic interactions. Applicants traverse.

The cited documents do not demonstrate that numerous obstacles exist for using polymeric compositions to deliver nucleic acids into cells.

The Examiner cites Finsinger and Choi to argue that there are a number of obstacles to overcome in using polymer complexes to deliver nucleic acid molecules into cells. Applicants respectfully disagree. In their specific contexts, both Finsinger and Choi show that having demonstrated that one member of a family of compounds is useful to deliver nucleic acids into cells, other members of the family work as well.

Finsinger uses polymer structures in non-viral gene delivery. In the excerpt of the Introduction cited by the Examiner, Finsinger states:

> Consequently, one major objective in nonviral vector development is to devise vectors which are inert in the in vivo environment during the delivery phase...In liposome and nanoparticle technology, **poly(ethylene glycol) has been used to confer to these drug carriers the desired stability during the extracellular delivery phase** (emphasis added).

Finsinger then concludes the Introduction by stating:

> We show that copolymers obtained with the peptides YE5C... and INF7...stabilize polyplexes at small size and protect from complement activation and opsonization. Finally, we demonstrate that protecting nonviral vectors with these copolymers is compatible with the cellular steps of gene delivery (page 1184, top of first column).

Thus, Finsinger provides no evidence that there are "many" obstacles to overcome in using polymer complexes for delivering DNA into cells once one member of a family is used successfully. In fact, Finsinger is evidence that its complexes represent an efficient and viable means for introducing nucleic acid molecules into cells.

Likewise, Choi fails to support the Examiner's contention that "many" obstacles must be overcome once one member of a family is shown to work successfully. The Choi excerpt to which the Examiner points, refers to gene delivery systems such as cationic liposomes. It does not refer to polymer complexes. When describing polymeric complexes, Choi recites a polymeric gene carrier complex for delivering nucleic acids into cells that is "safe and efficient" (see page 2, line 25). Accordingly, Choi, like Finsinger, in its specific context does

not provide evidence of unpredictability. Rather, both documents provide support for the efficacy of a claimed genus once a species is shown to work. The art, therefore, does not indicate that there are "many" obstacles that must be overcome in order to predictably deliver a nucleic acid into a cell using the polymer complexes of Finsinger or Choi.

Like Finsinger and Choi in the context of their delivery systems, the instant specification teaches that the claimed copolymer complexes deliver DNA to cells. See, e.g., page 14, lines 30-32, which states "The copolymer of the invention has the characteristic of sterically stabilising the nucleic acid-polycation complex and of reducing or inhibiting its undesired interaction with components of body fluids (e.g. serum proteins)." Also see Example 4, which teaches that the copolymers inhibit complement activation. Accordingly, like Finsinger and Choi, the specific teachings and illustrative examples of the instant application teach the skilled worker that the claimed complexes are an effective means of introducing nucleic acids into cells.

The specification enables the full scope of the claimed invention.

The working embodiments, accompanied by the more general teachings of the specification, enable the full scope of the claimed invention. The specification teaches how to produce various copolymers comprising different PEG molecules and different amino acid or peptide substituents for X. The same teachings are applicable to the other X substituents claimed and described on pages 6-7 of the specification, for example (see page 11, lines 5-6 of the specification). Indeed, MPEP 2164.01(b) states, "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." The specification therefore teaches how to produce the claimed copolymer having Formula I.

The specification also teaches that the claimed composition delivers nucleic acid molecules into cells (e.g., Examples 9-13, and 16-19). Regardless of whether or not the art has tested ionically bound copolymers (see Examiner's remarks on page 8 of the Office Action)[1], the instant application demonstrates that such copolymers are effective in delivering nucleic acid molecules into cells. The working embodiments are *illustrative examples* to

[1] Choi, in fact, does test polymers that electrostatically bind to nucleic acid (see Figure 1 of Choi, for example). The copolymer structure in Choi is, of course, different from the copolymer structure claimed in this invention (see Figure 2 in Choi).

confirm that the claimed composition, in its full scope, is a successful system for delivering nucleic acids into cells. Indeed, as taught in the specification, charged copolymers of general Formula I that coat (via ionic interactions) a nucleic acid-containing complex will exhibit the desired properties of sufficient solubility, stabilizing the complex, protecting the nucleic acids from opsonization, etc., regardless of the exact structure of the copolymer (see, e.g., lines 2-3 on page 4 and lines 30-32 on page 14). The specification, therefore, teaches the skilled artisan how to use the claimed composition to deliver nucleic acids into cells without undue experimentation. See MPEP 2164.02, which states:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.

Based on the teachings of this application and the level of skill in the art, no undue experimentation is required to obtain the claimed composition or to use the claimed composition to deliver nucleic acids into cells.

Applicants submit herewith a Declaration by Dr. Christian Plank ("Declaration"), which provides additional evidence that copolymers encompassed by general Formula I exhibit the desired activity of delivering nucleic acids into cells. The Declaration demonstrates that positively charged copolymers—in addition to the negatively charged copolymers exemplified in the Examples in the specification, as filed—are suitable to mediate nucleic acid delivery to cells.

The Declaration describes two positively charged copolymers that were produced according to the methods taught in the specification (see (7) of the Declaration). The Declaration also shows that the two copolymers formed complexes with DNA, and Exhibit B of the Declaration demonstrates that both copolymers were able to deliver DNA encoding the luciferase reporter gene into HeLa cells.

Accordingly, the Declaration confirms that copolymers with different chemical and physical properties but that are encompassed by the general Formula I form complexes with DNA and deliver DNA into cells. Further, the Declaration confirms that the skilled worker, based on the teachings of the specification, would be able to obtain the claimed compositions and practice the claimed methods, in their full scope, without undue experimentation.

For at least the reasons discussed above, the claimed invention is enabled for its full scope. The working embodiments provided in the specification and in the Declaration are illustrative examples that show that ionically bound polymeric complexes successfully deliver nucleic acids into cells. The application therefore complies with the enablement requirement. Applicants request that the Examiner reconsider and withdraw this rejection.

35 U.S.C. § 112, second paragraph

Claims 1-11, 13, 14, and 16-18 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner contends that the terms "homo- or hetero-bifunctional derivative" of an amphiphilic polymer, and "amino acid derivative," "peptide derivative," and "spermidine derivative," are not defined in the specification and are not art-recognized terms. Applicants traverse.

The term "derivative" as it applies to a molecule is an art-recognized term that typically refers to, in chemistry, "a compound derived or obtained from another and containing essential elements of the parent substance" (see http://www.thefreedictionary.com/derivative) or "a compound that is formed from a similar compound or a compound that can be imagined to arise from another compound, if one atom is replaced with another atom or group of atoms" (see http://en.wikipedia.org/wiki/Derivative_(chemistry)). Also see http://www.biology-online.org/dictionary/Derivative, which defines "derivative" as a "chemical substance derived from another substance either directly or by modification or partial substitution". The term "derivative" as it applies to a specified molecule or chemical substance is therefore an art-recognized term that has clear meaning in the field of chemistry, namely to refer to compounds that differ from a given first compound by modifications of one or more peripheral structures without affecting the backbone structure of the first compound. The term's usage in the specification is consistent with these definitions and with how the term is generally used in the art. Accordingly, the skilled artisan would readily envision derivatives of amphiphilic polymers, amino acids, peptides, and spermidine.

The specification also further describes derivatives of the claimed invention:

An amino acid derivative:

> ...an amino acid derivative may also be used for the synthesis, **the amino acid derivative having two functional groups for the copolymerization with the polymer and being obtained by modification of an amino acid...with a linker grouping for coupling with the effector molecule**" (emphasis added) (page 7, lines 28-31).

A peptide derivative:

> ...X can be **a peptide derivative, wherein the modification of the peptide is a charged grouping which is different from an amino acid**; examples of such groupings are sulfonic acid groupings or charged carbohydrate groups such as neuraminic acids or sulfated glycosaminoglycans" (emphasis added) (page 8, lines 25-28).

Also see page 8, line 12 to page 9, line 14, and lines 29-31 on page 10, for example, which further describe derivatives of the invention.

Accordingly, a "derivative" as used in the specification refers to a compound derived or obtained from another by modification or partial substitution (see definitions above). The skilled artisan—based on the general use of the term "derivative" in the field of organic chemistry and in the specification—would, therefore, understand the metes and bounds of the claimed invention. For all of these reasons, the claimed invention complies with 35 U.S.C. § 112, second paragraph. Applicants request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

In view of at least the foregoing remarks, applicants submit that the pending claims are in condition for allowance and respectfully request favorable reconsideration. Applicants have authorized the Director in the accompanying Transmittal Form to charge any fees required, in addition to the extension of time fee, to Deposit Account No. 06-1075 under Order No. 003747-0061.

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